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RESEARCH ARTICLE

Safety and efficacy of the partial adenosine A1 receptor agonist neladenoson bialanate in patients with chronic heart failure with reduced ejection fraction: a phase IIb, randomized, double-blind, placebo-controlled trial

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Aims Neladenoson bialanate is a partial adenosine A1 receptor agonist with demonstrated beneficial effects on cardiac function in animal models. We aimed to assess the dose–response effect of neladenoson bialanate on cardiac structure and function, clinical outcome, and safety in patients with heart failure (HF) with reduced ejection fraction (HFrEF).

Methods and results PANTHEON was a dose-finding, phase IIb, randomized, double-blind, placebo-controlled trial conducted in 92 centres in 11 countries including 462 patients with chronic HFrEF, randomized to once daily oral dose of neladenoson bialanate (5, 10, 20, 30, and 40 mg) or placebo. The primary endpoints were change from baseline to 20 weeks in left ventricular ejection fraction (LVEF) (echocardiography) and in N-terminal pro-B-type natriuretic peptide (NT-proBNP). Mean age of the patients was 67 years, 17% were female, mean LVEF was 28%, mean NT-proBNP was 2085 ng/L. After 20 weeks of treatment, there was no dose–effect of neladenoson bialanate on changes in NT-proBNP or LVEF (primary endpoints). No effect of neladenoson bialanate was found on left ventricular volumes, high-sensitivity troponin T, or cardiovascular mortality, HF hospitalization, and urgent visits for HF (secondary endpoints). There was a dose-dependent increase in creatinine and cystatin C, and a dose-dependent decrease in estimated glomerular filtration rate and heart rate.

Conclusions In patients with chronic HFrEF, treatment with neladenoson bialanate was not associated with dose-dependent favourable effects on cardiac structure and function, cardiac risk markers, or clinical outcome but was associated with a dose-dependent decrease in renal function.
Clinical Trial Registration: ClinicalTrials.gov identifier NCT02992288.

Keywords Heart failure • Adenosine • Partial adenosine A1 agonist • Cardiac contractility • Renal function

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Introduction

Adenosine is ubiquitously present in the entire body and is activated in response to stress to protect against organ and tissue damage. In the heart, activation of adenosine A1 receptors modulates ischaemic injury, arrhythmogenesis, coronary and ventricular dysfunction, apoptosis, mitochondrial dysfunction, and ventricular remodelling.[1] Heart failure (HF) with reduced ejection fraction (HFrEF) is characterized by impaired mitochondrial function and impaired calcium handling due to a decreased activity of sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2a). Activation of adenosine A1 receptors in the heart results in improved mitochondrial function and sarcoplasmic SERCA2 activity and modulates energy substrate utilization.[2] Therefore, adenosine A1 receptor agonists may be beneficial in patients with HF. Full A1 receptor agonists can provoke undesired cardiac effects, in particular higher degree atrioventricular (AV) blocks. In addition, full adenosine A1 receptor agonists can impair renal function due to vasoconstriction of the afferent arterioles.[3] Partial agonists might limit the undesired cardiac conduction disorders and renal effects while preserving beneficial effects on the heart. Preclinical studies showed that a partial adenosine A1 receptor agonist improved cardiac function at doses that did not have undesirable effects on heart rate, AV conduction, and blood pressure.[1,4] The safety and tolerability of the partial adenosine A1 receptor agonist neladenoson bialanate was studied in two small pilot studies in patients with HFrEF.[5] In these studies, neladenoson bialanate was safe and well tolerated without second- or third-degree AV blocks or reduction of renal function. The present phase II study was designed to evaluate the effects of neladenoson bialanate on cardiac structure and function, clinical outcome, and safety in patients with HFrEF.

Methods

Study design

PANTHEON was a multicentre, randomized, placebo-controlled, parallel-group, double-blind, dose-finding phase 2 trial to study the efficacy, safety, pharmacokinetic and pharmacodynamic effects of the oral partial adenosine A1 receptor agonist neladenoson bialanate over 20 weeks in subjects with chronic HFrEF. The study design has been previously reported.[6] The protocol is presented in online supplementary *Methods S1* and the statistical analysis plan in online supplementary *Methods S2*. The trial was approved by the ethics committee at each study centre. All the patients provided written informed consent. This trial was registered with ClinicalTrials.gov, identifier NCT02992288.

Patient population

The complete list of inclusion and exclusion criteria were published previously.[6] In brief, eligible patients had stable chronic HF with a left ventricular ejection fraction (LVEF) $\leq$35% and either (i) an episode of worsening HF within 3 months prior to enrolment with B-type natriuretic peptide (BNP) $\geq$100 pg/mL or N-terminal proBNP (NT-proBNP) $\geq$400 pg/mL (sinus rhythm) or BNP $\geq$300 pg/mL or NT-proBNP $\geq$1200 pg/mL (atrial fibrillation), or (ii) at any time in the past 4 weeks, had documented BNP $\geq$300 pg/mL or NT-proBNP $\geq$1200 pg/mL (sinus rhythm) or BNP $\geq$600 pg/mL or NT-proBNP $\geq$2400 pg/mL (atrial fibrillation). Main exclusion criteria were acute *de novo* HF and any cause of chronic HF other than ischaemic cardiomyopathy or idiopathic dilated cardiomyopathy.

Study endpoints

The complete list of study endpoints of PANTHEON has been published previously.[6] The primary endpoints were change in LVEF (%) as measured by echocardiography and in NT-proBNP between baseline and 20 weeks (end of treatment). The secondary endpoints were change in left ventricular end-systolic (LVESV) and end-diastolic volume (LVEDV) from baseline and high-sensitivity troponin T (hs-TnT) from baseline to 20 weeks, and cardiovascular (CV) mortality, HF hospitalization, and urgent visits for HF as clinical outcomes. Key exploratory endpoints were (i) weekly means of daily mean duration in hours, of hourly intensity in gravitational units, of daily mean intensity in percentage, of daily maximum intensity in percentage (measured with the AVIVO™ patch); (ii) change in renal function, and (iii) change in quality of life, measured by both the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the EuroQol 5 dimensions instrument (EQ-5D-5L).

The Medtronic AVIVO™ Mobile Cardiac Telemetry System provides continuous monitoring of symptomatic and asymptomatic cardiac arrhythmias and was implemented as a safety monitoring tool for this trial. The device is also equipped with an accelerometer and measures patient's physical activity in an hourly basis. Activity outputs were reported in gravitational unit and as a percentage of the patient's activity intensity compared to that of a healthy young male volunteer. The patch was applied to the patient's chest for seven consecutive days: at screening and four times during treatment (baseline, week 4, week 8, and week 19).

Statistical analysis

To evaluate the primary and secondary outcomes in both studies, we combined a multiple comparison procedure (MCP) with modelling techniques under model uncertainty (the MCP-Mod approach) in two key steps.[6,7] Step 1 was a one-sided multiple contrast test for a non-flat, favourable dose–response curve while controlling for type 1 error ($\alpha = 5\%$). A set of five candidate shapes (a linear model, an Emax model, sigmoidal Emax models 1 and 2, and a quadratic model) was pre-defined to cover both plausible and diverse dose–response profiles. Step 2 was the estimation step: if a dose–response signal was established in step 1, a dose–response model and target dose(s) of interest was to be estimated. A dose–response signal is shown in the primary efficacy analysis if at least one of the two null hypotheses related to the primary efficacy variables can be rejected. The Hochberg (step-up) procedure was applied to control the family-wise error rate. No multiplicity adjustment was done in analysis for further efficacy or safety variables.

Based on the assumption of a maximum effect for absolute increase in LVEF of 5% for a dose of neladenoson bialanate, an absolute increase of $\leq$2% under placebo, and a standard deviation of 7%, an overall sample size of 288 randomly allocated patients (using a 1:2:2:2:2:3 allocation ratio corresponding to the neladenoson bialanate 5, 10, 20, 30, and 40 mg dose groups and placebo) was required to ensure a minimum power of 80% to detect the presence of a dose–response relationship.

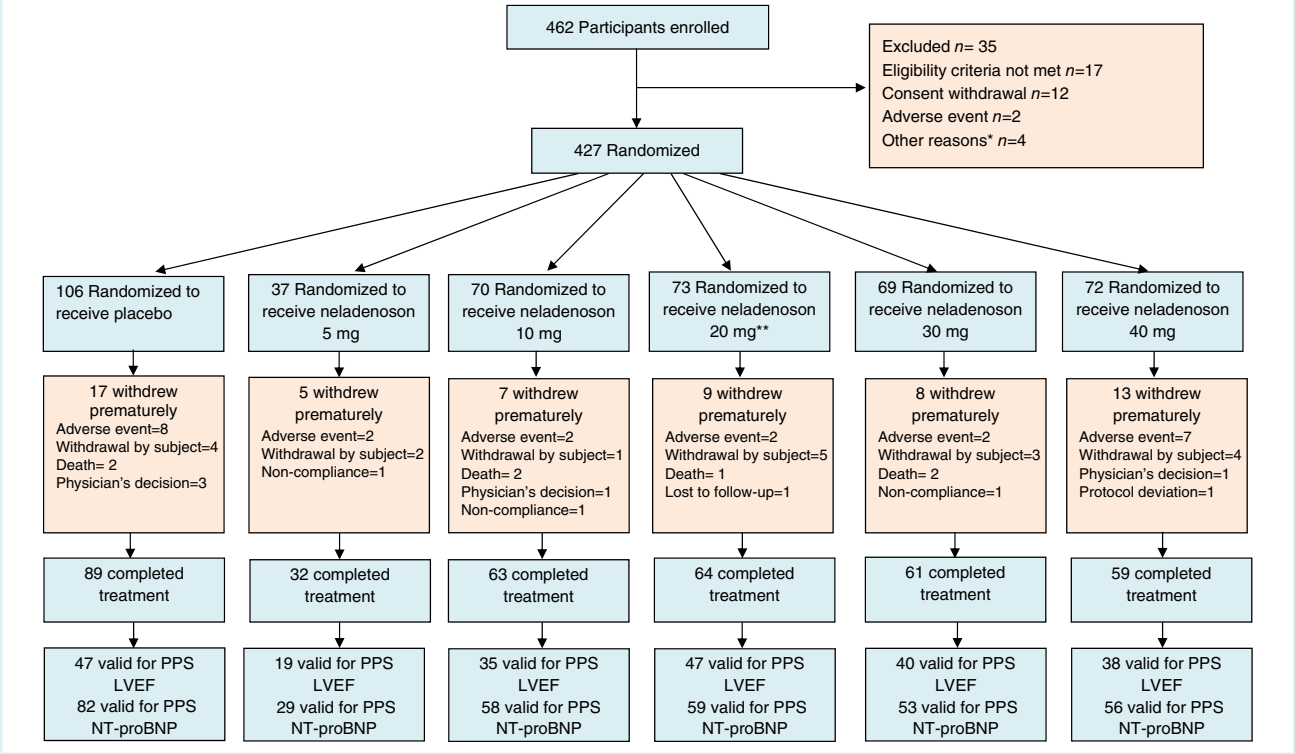


Figure 1 Consort diagram. LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PPS, per-protocol set. *Other reasons were: logistical difficulties, physician decision, and technical problems. **One subject in the 20 mg arm never took study drug after randomization.

This power calculation was based on simulations that use all five candidate models considered for dose–response modelling. Taking into account both primary outcomes in PANTHEON, simulations showed that the power to reject at least one of the two primary null hypotheses was 83%. The primary analysis of primary and secondary endpoints was performed on the respective per-protocol sets (PPS). Subjects were excluded from both PPS if they presented validity findings. For the LVEF PPS and NT-proBNP PPS, subjects without baseline or end-of-treatment values for LVEF and NT-proBNP, respectively, were excluded with the exception of 'compliant and adherent' patients who were 'censored' due to CV death or a hospitalization for HF preventing the assessment of the relevant efficacy endpoints 20 weeks after randomization to take place as planned. For missing post-baseline value due to CV death or study drug/study discontinuation due to HF, a worst case approach was applied, i.e. for each dose group the worse observed value (WOV) in that group was entered as post-baseline value.[8]

The LVEDV and LVESV results were also analysed in the LVEF PPS. The missing values of post-baseline of LVESV and LVEDV were imputed by WOV if the baseline values were not missing and the subjects have CV death or HF hospitalization, otherwise remained missing. Hs-TnT values were analysed in the NT-proBNP PPS. Similarly as for the primary efficacy variables and for LVESV and LVEDV, the missing values of post-baseline of hs-TnT were imputed by WOV if the baseline values were not missing and the subjects had CV death or HF hospitalization, otherwise remained missing. The distribution of subjects PPS and per-dose group is displayed in *Figure 1*. Post-hoc analysis on exploratory parameters described in this document was performed in the full analysis set including all patients randomized and using the last observation carried forward approach for missing data. Analysis of safety data was performed on the safety analysis set including all patients who took at least one dose of study drug, without imputation.

Data sharing statement

Bayer has granted Groningen University access to anonymized patient level data from the neladenoson bialanate phase IIb clinical studies, via the Access System, as described in the data sharing agreement (online supplementary *Methods S3*).

Results

Patients

From 22 February 2017 to 28 March 2018, a total of 462 patients were enrolled at 92 centres in 11 countries (USA, Belgium, Germany, Greece, Italy, Netherlands, Spain, Bulgaria, Poland, Israel, and Japan –for the complete list of participating sites and principal investigators see online supplementary *Methods S4*). A total of 35 patients were excluded as screen failures, mostly related to violation of eligibility criteria. Accordingly, 427 patients were randomized to neladenoson bialanate 5, 10, 20, 30, and 40 mg dose groups or placebo (*Figure 1*). *Table 1* shows that the groups were balanced with respect to baseline characteristics. Mean age of the patients was 67 years, 17% was female, mean LVEF was 28%, median NT-proBNP was 2085 ng/L, 62% had ischaemic HF, 38%

Table 1 Baseline characteristics

Characteristic	Placebo (*n* = 106)	Neladenoson bialanate					Total (*n* = 427)
		5 mg (*n* = 37)	10 mg (*n* = 70)	20 mg (*n* = 73)	30 mg (*n* = 69)	40 mg (*n* = 72)	
Age (years)	66.9	66.6	66.4	68.1	67.6	67.5	67.2
Female sex	18 (17.0%)	9 (24.3%)	11 (15.7%)	14 (19.2%)	12 (17.4%)	7 (9.7%)	71 (16.6%)
Race							
White	98 (92.5%)	32 (86.5%)	65 (92.9%)	66 (90.4%)	64 (92.8%)	65 (90.3%)	390 (91.3%)
Black	2 (1.9%)	2 (5.4%)	2 (2.9%)	2 (2.7%)	2 (2.9%)	2 (2.8%)	12 (2.8%)
Asian	6 (5.7%)	3 (8.1%)	3 (4.3%)	5 (6.8%)	3 (4.3%)	5 (6.9%)	25 (5.9%)
Region							
North America	4 (3.8%)	4 (10.8%)	6 (8.6%)	1 (1.4%)	3 (4.3%)	4 (5.6%)	22 (5.2%)
Western Europe and Israel	57 (53.8%)	15 (40.5%)	27 (38.6%)	38 (52.1%)	45 (65.2%)	40 (55.6%)	222 (52.0%)
Eastern Europe	39 (36.8%)	15 (40.5%)	35 (50.0%)	29 (39.7%)	18 (26.1%)	23 (31.9%)	159 (37.2%)
Asia	6 (5.7%)	3 (8.1%)	2 (2.9%)	5 (6.8%)	3 (4.3%)	5 (6.9%)	24 (5.6%)
Vital signs							
SBP (mmHg, mean)	117.3	117	117.5	119.6	121.5	117.6	118.5
HR (bpm, mean)	70.1	69.3	70	69.8	68.3	70.7	69.8
BMI (kg/m^2, mean)	27.8	28.3	28.5	27	27.9	28.5	27.9
GFR (ml/min/1.73 m^2, mean)	61.8	60.7	60.5	63.2	58.9	59.8	60.2
Clinical features of HF							
LVEF (%)	28.24	26.22	27.58	29.7	29.87	26.24	28.18
NT-proBNP (pg/mL, median)	2111	2071	2063	1894.5	2084	2419	2085
NYHA class I	0	0	1 (1.4%)	0	0	0	1 (0.2%)
NYHA class II	62 (58.5%)	23 (62.2%)	38 (54.3%)	44 (60.3%)	49 (71.0%)	49 (68.1%)	265 (62.1%)
NYHA class III/IV	44 (41.5%)	14 (37.8%)	31 (44.3%)	29 (39.7%)	20 (29.0%)	23 (31.9%)	161 (37.7%)
Ischaemic cardiomyopathy	65 (61.3%)	25 (67.6%)	45 (64.3%)	50 (68.5%)	37 (53.6%)	42 (58.3%)	264 (61.8%)
Medical history							
Hypertension	63 (59.4%)	22 (59.5%)	39 (55.7%)	47 (64.4%)	40 (58.0%)	44 (61.1%)	255 (59.7%)
Diabetes mellitus	45 (42.5%)	15 (40.5%)	23 (32.9%)	36 (49.3%)	23 (33.3%)	26 (36.1%)	168 (39.3%)
Atrial fibrillation	44 (41.5%)	14 (37.8%)	27 (38.6%)	26 (35.6%)	27 (39.1%)	33 (45.8%)	171 (40.0%)
Concomitant medication of interest (%)							
ACEi	55	51	59	56	52	63	56
ARB	14	16	16	19	13	13	15
ARNI	19	19	13	12	17	17	16
MRA	88	89	80	82	81	79	83
Beta-blocker	97	100	94	96	97	96	97
Loop diuretics	94	92	94	95	91	96	94
Ivabradine	7	11	10	7	9	13	9
CRT-D	11	16	18	20	20	17	17
ICD	34	30	31	22	22	21	27

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; CRT-D, cardiac resynchronization therapy with defibrillation; GFR, glomerular filtration rate; HF, heart failure; HR, heart rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.

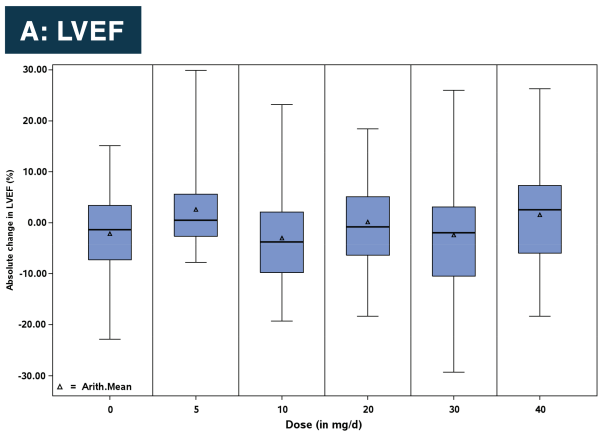
had dilated cardiomyopathy, 62% had New York Heart Association (NYHA) class II symptoms, 40% had a history of atrial fibrillation, and 39% had diabetes. Patients were optimally treated at baseline (87% renin–angiotensin–aldosterone system inhibitors, 97% beta-blockers, and 83% mineralocorticoid receptor antagonists).

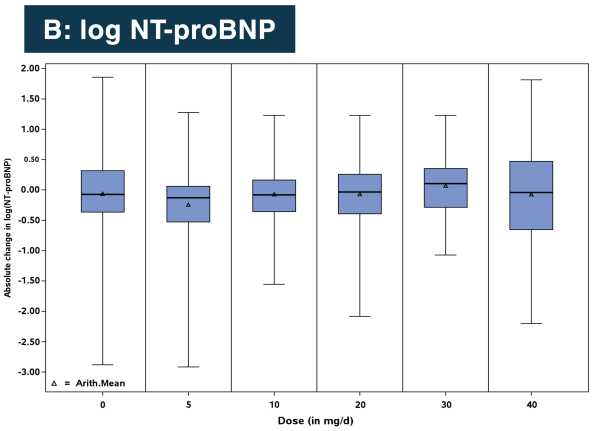
Primary endpoints

Results of the primary endpoint are presented in *Figure 2*. The per-protocol analysis of LVEF was done in 226 patients since the rest of the echocardiograms were either missing or of poor quality. Compared with placebo, there was no dose–response effect of neladenoson bialanate on the change in LVEF ($P = 0.23$; lowest *P*-value for the linear candidate model shape). For the per-protocol analysis of the change in NT-proBNP, 337 patients were available with valid measurement both at baseline and at week 20. Compared with placebo, there was no dose–response effect of neladenoson bialanate on the change in NT-proBNP ($P = 0.74$ lowest *P*-value for the Emax candidate model shape).

Secondary endpoints

Results of the change in LVESV, LVEDV and hs-TnT are presented in online supplementary *Figure S1*. Overall, left ventricular volumes





Dose-response tests for absolute change in LVEF (%) from baseline to Week 20 (PPS LVEF)

Model	Estimate	Standard error	t-statistic	Degrees of freedom	Adjusted p-value
Linear	1.6447	1.5025	1.0946	220	0.2297
Sig Emax 1	0.7794	1.4828	0.5257	220	0.4409
Sig Emax 2	1.4188	1.5245	0.9307	220	0.2842
Emax	1.4348	1.4045	1.0215	220	0.2534
Quadratic	0.9598	1.4417	0.6657	220	0.3842

Dose-response tests for absolute change in log-transformed NT-proBNP from baseline to Week 20 (PPS NT-proBNP)

Model	Estimate	Standard error	t-statistic	Degrees of freedom	Adjusted p-value
Linear	-0.0693	0.0838	-0.8269	331	0.8966
Sig Emax 1	-0.0811	0.0824	-0.984	331	0.9233
Sig Emax 2	-0.088	0.0856	-1.0276	331	0.9296
Emax	-0.0172	0.0766	-0.2248	331	0.7357
Quadratic	-0.0714	0.08	-0.8915	331	0.9083

Figure 2 Primary endpoints. Change in (*A*) left ventricular ejection fraction (LVEF) and (*B*) N-terminal pro-B-type natriuretic peptide (NT-proBNP). Box: 25th–75th percentile; horizontal line: median; circle: arithmetic mean; vertical lines extend from the box to a distance of at most 1.5 interquartile ranges and any value more extreme is plotted separately. PPS, per-protocol set.

decreased during the 20 weeks of the study in all treatment arms, the decrease was more evident in the 5 and the 40 mg groups for both LVESV (21 mL and 15 mL, respectively) and LVEDV (21 mL and 19 mL, respectively), whereas the other dose groups showed less decrease compared to placebo where a mean decrease of 5 mL in LVESV and of 13 mL in LVEDV was observed. There was no dose–response effect of neladenoson bialanate on the change in LVESV ($P = 0.46$ lowest *P*-value for the linear candidate model shape) and LVEDV ($P = 0.57$ lowest *P*-value for the linear candidate model shape). Results of log-transformed hs-TnT showed no decreasing dose–response relationship ($P = 0.99$ lowest *P*-value for the SigmoidalEmax2 candidate model shape). The time to the composite clinical event of CV death and hospitalization or urgent visit for HF is presented in *Figure 3*. Although the highest event rate was observed in patients receiving placebo, and the lowest event rate was observed in patients receiving the highest (40 mg) dose of neladenoson bialanate, in the full analysis set, this difference was numerically small and not statistically significant.

Exploratory endpoints

Activity

Activity was measured by the AVIVO device and analysis was performed on the weekly mean activity intensity assessed in gravitational units as well as assessed in percentage of the activity of a healthy male; and weekly activity duration in hours. No changes from baseline in either duration or intensity of activity across any doses were noted.

Echocardiography

Exploratory analyses revealed that the percentage of patients with an increase in LVEF ≥ 5 points compared to baseline was higher in the active arms vs. placebo. However, no dose-dependent trend was observed. In addition, a decrease in mitral valve E wave peak velocity in the active arms compared to placebo was noted, but the decrease was not dose-dependent. The remaining relevant echocardiography parameters showed no dose-dependent change.

Renal function

We observed a dose-dependent decrease in renal function with increasing doses of neladenoson bialanate. Online supplementary *Figure S2* shows a statistically significant dose-dependent decrease in estimated glomerular filtration rate (eGFR) between baseline and 20 weeks of treatment ($P = 0.0014$ in the linear candidate model shape). In addition, when eGFR was depicted against the measured plasma concentration of BAY 84-2174, we found an exposure dependent decrease in eGFR with increasing plasma concentrations of BAY 84-2174. Similarly, plasma cystatin C was increased in all dosages vs. placebo and this increase was exposure-dependent as well.

Quality of life

We observed a borderline nominally significant dose-dependent ($P = 0.04$ for the linear candidate model shape) improvement of approximately four points compared to placebo in the KCCQ Overall Summary Score. This change from baseline

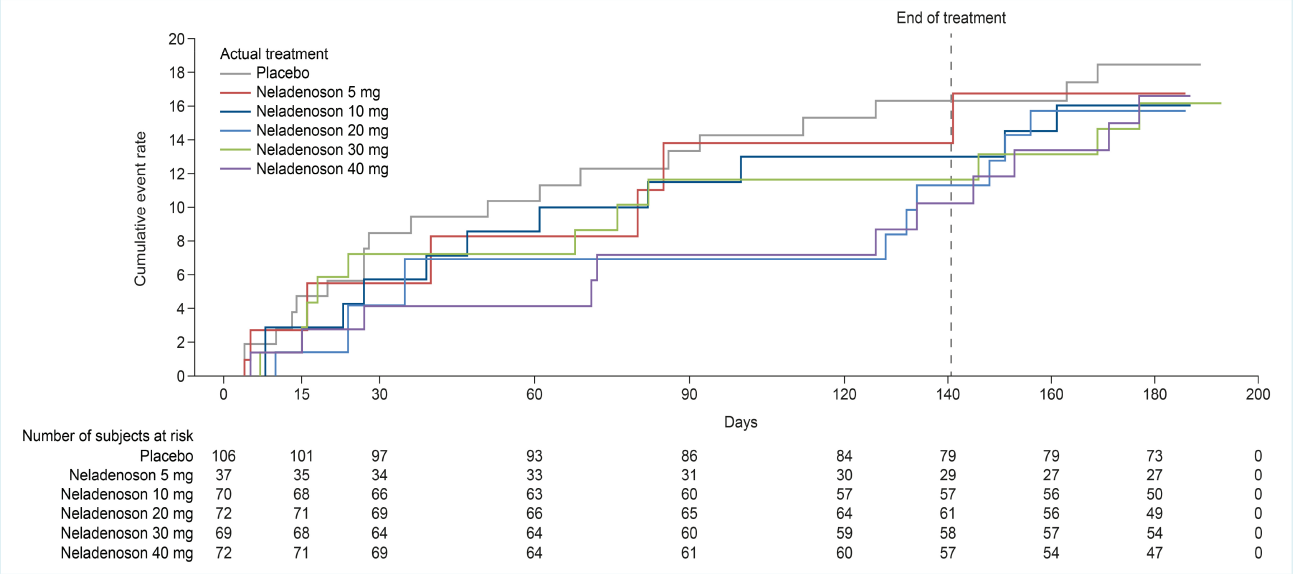


Figure 3 Kaplan–Meier survival curves of the composite clinical endpoint of cardiovascular death and hospitalization or urgent visit for heart failure.

was exposure-dependent. The observed change was mainly driven by the social limitation domain and to a lesser extent by physical limitation domain. We found no dose-dependent change in the EQ-5D-5L visual analogue scale score.

Safety

Safety data are presented in *Table 2*. The incidence rates of adverse events (AE), drug-related AEs, serious AEs and drug-related serious AEs in subjects treated with placebo or neladenoson bialanate were similar in all groups. The majority of AEs and drug-related AEs in all groups were of mild to moderate intensity. We found numerically less deaths in the pooled neladenoson bialanate group (3.4%) vs. placebo (6.6%). Hypotension was reported more frequent in the pooled neladenoson bialanate groups (5.6%) vs. placebo (0.9%). There was no exposure-dependent change in systolic blood pressure, but a modest yet statistically significant decrease in diastolic blood pressure with increasing plasma concentrations of BAY 84-2174 ($P = 0.0055$) was noted. The proportion of subjects with AEs 'renal impairment' was higher in the pooled neladenoson group (8.4%) vs. placebo (5.7%) and serious AEs belonging to the renal and urinary disorders group were also more frequently reported in the pooled neladenoson bialanate groups (5.9%) vs. placebo (3.8%), corroborating with both findings of dose-dependent decrease in eGFR and increase in cystatin C. There were three complete AV blocks in the pooled neladenoson bialanate groups and none in the placebo group. No symptomatic bradycardias were reported. There were no clinically relevant differences in the groups with regard to PR duration, QTc prolongation, ventricular tachyarrhythmias (online supplementary *Table S1*). However, on a post-hoc analysis performed with last observation carried forward for missing data, we found a statistically significant dose-related ($P = 0.0016$ in the Emax candidate model shape) decrease in heart rate from baseline to week 20 (online supplementary *Figure S3*). A decrease of an average of 2 bpm at the 40 mg dose group was demonstrated by the AVIVO monitoring device assessing weekly measures of 5 min intervals during day time from screening (i.e. the week prior to study drug intake) to the last week of treatment (week 19) (online supplementary *Table S2*), however no dose-dependent trend could be observed in this descriptive analysis.

The study drug was discontinued in 59 participants (13.8%) in total. Treatment discontinuation rate was highest in the 40 mg group (13 participants, 18%), followed by the placebo group (17 participants, 16%). The 5 mg group had 5 (13.5%) discontinuations, followed, in decreasing order, by the 20 mg ($n = 9$; 12%), 30 mg ($n = 8$; 11%), and 10 mg ($n = 7$; 10%) groups. Overall there was no pattern of AEs leading to discontinuation among the study groups.

Discussion

PANTHEON tested the hypothesis that the partial adenosine A1 receptor agonist neladenoson bialanate improves cardiac function and thereby reduces levels of NT-proBNP in patients with HFrEF. However, PANTHEON demonstrated no dose-dependent improvements in LVEF and NT-proBNP nor any other effects on left ventricular volumes or hs-TnT or cardiovascular mortality, HF hospitalization, and urgent visits for HF. We observed a dose-dependent decrease in renal function and heart rate, and a modest decrease in (diastolic) blood pressure. Therefore, the hypothesis that a partial adenosine A1 receptor agonist limits undesired cardiac conduction and renal disorders compared to a full agonist, while preserving its effects on cardiac function, must be rejected.

Table 2 Adverse events and serious adverse events in patients treated with placebo or neladenoson bialanate, 5–40 mg/day, by medical dictionary for regulatory activities version 21.0 preferred term

Events		Neladenoson bialanate					Total
	Placebo ($n = 106$)	5 mg ($n = 37$)	10 mg ($n = 70$)	20 mg ($n = 72$)	30 mg ($n = 69$)	40 mg ($n = 72$)	($n = 426$)
Any adverse events	71 (67.0%)	28 (75.7%)	48 (68.6%)	47 (65.3%)	53 (76.8%)	56 (77.8%)	303 (71.1%)
Mild	29 (27.4%)	15 (40.5%)	16 (22.9%)	20 (27.8%)	21 (30.4%)	24 (33.3%)	125 (29.3%)
Moderate	27 (25.5%)	11 (29.7%)	21 (30.0%)	22 (30.6%)	20 (29.0%)	22 (30.6%)	123 (28.9%)
Severe	15 (14.2%)	2 (5.4%)	11 (15.7%)	5 (6.9%)	12 (17.4%)	10 (13.9%)	55 (12.9%)
Any serious adverse events	31 (29.2%)	13 (35.1%)	28 (40.0%)	22 (30.6%)	28 (40.6%)	26 (36.1%)	148 (34.7%)
Any drug-related adverse events	14 (13.2%)	7 (18.9%)	10 (14.3%)	12 (16.7%)	7 (10.1%)	11 (15.3%)	61 (14.3%)
Any drug-related serious adverse events	4 (3.8%)	0	1 (1.4%)	3 (4.2%)	1 (1.4%)	1 (1.4%)	10 (2.3%)
Any adverse events resulting in death	7 (6.6%)	1 (2.7%)	5 (7.1%)	1 (1.4%)	2 (2.9%)	2 (2.8%)	18 (4.2%)
Discontinued due adverse events	8 (7.5%)	1 (2.7%)	2 (2.9%)	2 (2.8%)	2 (2.9%)	7 (9.7%)	22 (5.2%)
Discontinued due to serious adverse events	5 (4.7%)	0	2 (2.9%)	0	1 (1.4%)	4 (5.6%)	12 (2.8%)
Renal and urinary disorders	4 (3.8%)	2 (5.4%)	2 (2.9%)	3 (4.2%)	3 (4.3%)	9 (12.5%)	23 (5.4%)
Acute kidney injury	2 (1.9%)	0	0	1 (1.4%)	1 (1.4%)	2 (2.8%)	6 (1.4%)
Chronic kidney disease	2 (1.9%)	1 (2.7%)	0	0	0	2 (2.8%)	5 (1.2%)
Renal failure	0	0	0	1 (1.4%)	0	2 (2.8%)	3 (0.7%)
Renal impairment	0	1 (2.7%)	2 (2.9%)	1 (1.4%)	2 (2.9%)	3 (4.2%)	9 (2.1%)
Adverse events occurring in ≥4% patients overall							
Cardiac failure	22 (20.8%)	7 (18.9%)	12 (17.1%)	7 (9.7%)	11 (15.9%)	13 (18.1%)	72 (16.9%)
Renal impairment	6 (5.7%)	2 (5.4%)	2 (2.9%)	5 (6.9%)	8 (11.6%)	10 (13.9%)	33 (7.7%)
Hypotension	1 (0.9%)	1 (2.7%)	6 (8.6%)	5 (6.9%)	3 (4.3%)	3 (4.2%)	19 (4.5%)
Ventricular tachycardia	4 (3.8%)	2 (5.4%)	3 (4.3%)	3 (4.2%)	3 (4.3%)	2 (2.8%)	17 (4.0%)
Adverse events leading to discontinuation in >1 subject							
Cardiac failure	3 (2.8%)	0	2 (2.9%)	0	0	1 (1.4%)	5 (1.2%)
Headache	1 (0.9%)	1 (2.7%)	0	0	1 (1.4%)	0	3 (0.7%)
Hypotension	1 (0.9%)	0	0	1 (1.4%)	0	0	2 (0.5%)

Patients in PANTHEON reflected a typical stable chronic HF population. With a mean LVEF of 28% and a mean NT-proBNP of 2085 ng/L, there was sufficient room for improvement of both primary outcomes with neladenoson bialanate. However, the analysis of LVEF as a primary outcome in the PPS was limited by the high number of missing echocardiograms or those of insufficient quality. Patients in PANTHEON were treated according to current HFrEF guidelines, with 87% on a renin–angiotensin–aldosterone system inhibitor, 97% on a beta-blocker, and 83% on a mineralocorticoid receptor antagonist.

The dose-related impairment in renal function was a consistent finding with multiple renal function parameters. Estimated GFR was reduced up to a mean of −9 mL/min/1.73 m^2 in the highest dose. This decrease in eGFR is likely related to adenosine A1 receptor activation in the kidney, which is responsible for modulation of the tubulo-glomerular feedback at the level of the *macula densa*.[3] Through renal *vas afferens* contraction, adenosine causes a decrease in renal blood flow. Adenosine A1 antagonists have consistently shown to improve renal function in smaller clinical mechanistic studies,[9] but the adenosine A1 receptor antagonist rolofylline failed to improve renal function and clinical outcome in a large phase II trial.[10]

A mean decrease in heart rate of up to 3–4 bpm was observed in the neladenoson bialanate groups compared to placebo. This decrease, however, did not correlate with higher reporting of symptomatic bradycardia in any treatment arm. A decrease in heart rate with neladenoson bialanate was expected, since it is a well-known effect of adenosine.

We found a modest, but statistically significant dose-dependent improvement in quality of life, when measured by the Overall Summary Score of the KCCQ. However, in contrast to what was expected, this result was mainly driven by the Social Score and not by the Symptoms Score. In addition, the data were inconsistent with the quality of life data from the EQ-5D-5L questionnaire. We therefore believe that this was a chance finding.

The most frequently reported AE in this study was worsening HF, and the distribution of such events was numerically similar in all treatment groups with slightly lower incidence in the active arms in comparison to the placebo group. However, the incidence of worsening renal function was more frequently reported in the two higher dose groups in comparison to placebo, which reflects the increase in creatinine previously described. AEs of special safety interest were defined as second-degree AV block leading to change in therapy or discontinuation of study drug, third-degree AV block, or symptomatic bradycardia. Only very few of those events were reported without any significant difference between groups.

PANTHEON was conducted based on the reported beneficial mechanistic cardiac effects of adenosine, the beneficial cardiac effects of a partial adenosine A1 receptor agonist in a dog model,[4]

and the finding that neladenoson bialanate appeared to be safe in two small early phase studies in patients with HF.[5] Partial adenosine A1 agonism was expected to maintain the beneficial cardiac effects while avoiding the deleterious effects on renal function and AV conduction. Unfortunately, beneficial cardiac effects could not be demonstrated while we observed a consistent impairment in renal function. The discrepancy between outcomes in animal models compared to clinical studies is well known, and was observed with this agent as well. This discrepancy might be related to several factors, such as pre-existent disease (e.g. atherosclerosis), co-morbidities, and background therapies. Taken together, these data do not support further development of partial adenosine A1 receptor agonists for the treatment of HFrEF.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Methods S1. Trial protocol.

Methods S2. Statistical analysis plan.

Methods S3. Data sharing agreement.

Methods S4. Participating sites, their principal investigators and recruitment.

Figure S1. Secondary endpoints: change in (*A*) left ventricular end-systolic volume, (*B*) left ventricular end-diastolic volume, and (*C*) high-sensitivity troponin T.

Figure S2. Emax dose–response model for the absolute change in estimated glomerular filtration rate from baseline to end of treatment (full analysis set).

Figure S3. Emax dose–response model for the absolute change in heart rate from baseline to end of treatment (full analysis set).

Table S1. Number of subjects with notifiable ECG findings triggered by system according to AVIVO (safety analysis set).

Table S2. Summary statistics for weekly average of daytime AVIVO heart rate (based on 5-min data) and absolute change from baseline to post-baseline (full analysis set).

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